

WHAT IS CLAIMED IS:

1. A modified human glycoprotein hormone comprising at least three basic amino acids in the  $\alpha$ -subunit at positions selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.
2. The modified human glycoprotein hormone of Claim 1, further comprising a fourth basic amino acid at a position selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.
3. The modified human glycoprotein hormone of Claim 2, wherein basic amino acids are at positions 11, 13, 16, and 20.
4. The modified human glycoprotein of Claim 2, wherein basic amino acids are at positions 11, 13, 17, and 20.
5. The modified human glycoprotein hormone of Claim 2, wherein basic amino acids are at positions 13, 14, 16, and 20.
6. The modified human glycoprotein hormone of Claim 2, wherein basic amino acids are at positions 13, 14, 17, and 20.
7. The modified human glycoprotein hormone of Claim 2, further comprising a fifth basic amino acid at a position selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.
8. The modified human glycoprotein hormone of Claim 7, wherein basic amino acids are at positions 13, 14, 16, 17, and 20.
9. The modified human glycoprotein hormone of Claim 7, wherein basic amino acids are at positions 11, 13, 14, 16 and 20.

10. The modified human glycoprotein hormone of Claim 1, wherein basic amino acids are at positions 11, 13, 14, 16, 17, and 20.

11. The modified human glycoprotein hormone of Claim 1, wherein basic amino acids are at positions 13, 16, and 20.

12. The modified human glycoprotein hormone of Claim 1, wherein the hormone is thyroid stimulating hormone.

13. The modified human thyroid stimulating hormone of Claim 12, wherein the modified hormone further comprises a basic amino acid in at least one position selected from the group consisting of positions 58, 63, and 69 of the b-subunit.

14. The modified human thyroid stimulating hormone of Claim 13, wherein the modified hormone comprises basic amino acids at positions 58, 63, and 69 of the b-subunit.

15. The modified human glycoprotein hormone of Claim 13, wherein a basic amino acid is at position 58.

16. The modified human glycoprotein hormone of Claim 13, wherein a basic amino acid is at position 63.

17. The modified human glycoprotein hormone of Claim 13, wherein a basic amino acid is at position 69.

18. The modified human glycoprotein hormone of Claim 1, wherein the hormone is follicle-stimulating hormone.

19. The modified human glycoprotein hormone of Claim 18, wherein the modified human glycoprotein hormone comprises a basic amino acid in at least one position selected from

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the group consisting of positions in the  $\beta$ -subunit of glycoprotein hormones, corresponding to positions 58, 63, and 69 of the  $\beta$ -subunit of the human thyroid stimulating hormone.

20. The modified human glycoprotein hormone of Claim 1, wherein the hormone is luteinizing hormone.

21. The modified human glycoprotein hormone of Claim 20, wherein the modified human glycoprotein hormone comprises a basic amino acid in at least one position selected from the group consisting of positions in the  $\beta$ -subunit of glycoprotein hormones, corresponding to positions 58, 63, and 69 of the  $\beta$ -subunit of the human thyroid stimulating hormone.

22. The modified human glycoprotein hormone of Claim 1, wherein the hormone is chorionic gonadotropin.

23. The modified human glycoprotein hormone of any of Claims 22, wherein the modified human glycoprotein hormone comprises a basic amino acid in at least one position selected from the group consisting of positions in the  $\beta$ -subunit of glycoprotein hormones, corresponding to positions 58, 63, and 69 of the  $\beta$ -subunit of the human thyroid stimulating hormone.

24. The modified human glycoprotein hormone of Claim 1, wherein the basic amino acids are lysine.

25. The modified human glycoprotein hormone of Claim 1, wherein the basic amino acids are selected from the group consisting of lysine and arginine.

26. A method of assisting reproduction in a subject comprising administering an assisting amount of the modified glycoprotein hormone of Claim 1.

27. A nucleic acid encoding the modified human glycoprotein hormone of Claim 1.

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28. A vector comprising the nucleic acid of Claim 27, wherein the vector is suitable for expressing the nucleic acid.

29. A host comprising the vector of Claim 28, wherein the host is suitable for expressing the nucleic acid.

30. The modified human glycoprotein hormone of Claim 1 further modified so that the modified human glycoprotein hormone has less than five amino acid substitutions in the  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

31. The modified glycoprotein hormone of Claim 1, wherein the modified human glycoprotein hormone has less than four amino acid substitutions in the  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

32. The modified glycoprotein hormone of Claim 1, wherein the modified human glycoprotein hormone has less than three amino acid substitutions in the  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

33. The modified glycoprotein hormone of Claim 1, wherein the modified human glycoprotein hormone has less than two amino acid substitutions in the  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

34. The modified glycoprotein hormone of Claim 1, wherein the hormone human glycoprotein hormone has the complete amino acid sequence homology with the human glycoprotein hormone in positions other than positions 11, 13, 14, 16, 17, and 20 of the  $\alpha$ -subunit.

35. A modified human glycoprotein hormone comprising a basic amino acid in the  $\alpha$ -subunit in at least one position selected from the group consisting of positions 11, 13, 14, 16, 17 and 20.

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36. The modified human glycoprotein hormone of Claim 35, wherein a basic amino acid is at position 11.
37. The modified human glycoprotein hormone of Claim 35, wherein a basic amino acid is at position 11.
38. The modified human glycoprotein hormone of Claim 35, wherein a basic amino acid is at position 14.
39. The modified human glycoprotein hormone of Claim 35, wherein a basic amino acid is at position 16.
40. The modified human glycoprotein hormone of Claim 35, wherein a basic amino acid is at position 17.
41. The modified human glycoprotein hormone of Claim 35, wherein a basic amino acid is at position 20.
42. The modified human glycoprotein hormone of Claim 35, wherein the basic amino acid is selected from the group consisting of lysine and arginine.
43. The modified human glycoprotein hormone of Claim 35, comprising a basic amino acid in at least two positions selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.
44. The modified human glycoprotein hormone of Claim 42, wherein the basic amino acids are at positions 16 and 20.
45. The modified human glycoprotein hormone of Claim 42, wherein the basic amino acids are at positions 16 and 13.
46. The modified human glycoprotein hormone of Claim 42, wherein the basic amino acids are at positions 20 and 13.

47. The modified human glycoprotein hormone of Claim 42, wherein the basic amino acid is selected from the group consisting of lysine and arginine.

48. The modified glycoprotein hormone of Claim 35, wherein the modified hormone is thyroid stimulating hormone.

49. The modified human thyroid stimulating hormone of Claim 48, wherein the modified hormone further comprises a basic amino acid in at least one position selected from the group consisting of positions 58, 63, and 69 of the b-subunit.

50. The modified human thyroid stimulating hormone of Claim 49, wherein the modified hormone comprises basic amino acids at positions 58, 63, and 69 of the b-subunit.

51. The modified human glycoprotein of Claim 49, wherein a basic amino acid is at position 58.

52. The modified human glycoprotein of Claim 49, wherein a basic amino acid is at position 63.

53. The modified human glycoprotein of Claim 49, wherein a basic amino acid is at position 69.

54. The modified glycoprotein of Claim 35, wherein the hormone is follicle-stimulating hormone.

55. The modified glycoprotein of Claim 35, wherein the hormone is luteinizing hormone.

56. The modified glycoprotein of Claim 35, wherein the hormone is chorionic gonadotropin.

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57. A method of treating a condition associated with a glycoprotein hormone activity in a subject comprising administering an effective amount of a suitable modified glycoprotein hormone of Claim 1 to the patient.

58. The method of Claim 56, wherein the condition is ovulatory dysfunction.

59. The method of Claim 56, wherein the condition is a luteal phase defect.

60. The method of Claim 56, wherein the condition is unexplained infertility.

61. The method of Claim 56, wherein the condition is male factor infertility.

62. The method of Claim 56, wherein the condition is time-limited conception.

63. The method of Claim 56, wherein the condition is thyroid carcinoma.

64. A method of assisting reproduction in a subject comprising administering an assisting amount of the modified glycoprotein hormone of Claim 35.

65. A nucleic acid encoding the modified human glycoprotein of Claim 35.

66. A vector comprising the nucleic acid of Claim 65, wherein the vector is suitable for expressing the nucleic acid.

67. A host comprising the vector of Claim 66, wherein the host is suitable for expressing the nucleic acid.

68. The modified human glycoprotein hormone of Claim 35 further modified so that the modified human glycoprotein hormone having less than five amino acid substitutions in the  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

69. The modified glycoprotein hormone of Claim 35, wherein the modified human glycoprotein hormone has less than four amino acid substitutions in the  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

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71. The modified glycoprotein hormone of Claim 35, wherein the modified human glycoprotein hormone has less than two amino acid substitutions in the  $\alpha$ -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

73. The modified human glycoprotein hormone of Claim 35, wherein the modified human glycoprotein hormone comprises a basic amino acid in at least one position selected from the group consisting of positions in the b-subunit of glycoprotein hormones other than the thyroid stimulating hormone, corresponding to positions 58, 63, and 69 of the b-subunit of the human thyroid stimulating hormone.

74. A modified human glycoprotein hormone having increased activity over the corresponding wild-type glycoprotein hormone, wherein the modified human glycoprotein hormone comprises a basic amino acid substituted at a position corresponding to the homologous amino acid position in a more active non-human glycoprotein hormone homolog.

75. A modified nonchimeric glycoprotein hormone from a particular species having increased activity over the corresponding wild-type glycoprotein hormone, wherein the modified glycoprotein hormone comprises a basic amino acid substituted at a position corresponding to the homologous amino acid position in a more active glycoprotein hormone homolog from another species.



76. The modified human glycoprotein hormone of Claim 74, wherein the non-human glycoprotein hormone homolog is a bovine glycoprotein hormone.

77. The modified human glycoprotein hormone of Claim 74, wherein the basic amino acid is lysine.

78. The modified human glycoprotein hormone of Claim 74, wherein the activity of the modified human glycoprotein hormone is increased by at least 3 fold.

79. A method of constructing superactive nonchimeric analogs of human glycoprotein hormones comprising:

- a) comparing the amino acid sequence of a more active homolog from another species to the human glycoprotein hormone;
- b) substituting amino acids in the human glycoprotein hormone with the corresponding amino acids from the homolog of the other species;
- c) determining the activity of the substituted human glycoprotein hormone; and
- d) selecting superactive analogs from the substituted human glycoprotein hormones.

80. A method of constructing antagonist nonchimeric analogs of human glycoprotein hormones, comprising:

- a) comparing the amino acid sequence of a less active homolog from another species to the human glycoprotein hormone;
- b) substituting amino acids in the human glycoprotein hormone with the corresponding amino acids from the other species;
- c) determining the activity of the substituted human hormone; and
- d) selecting antagonist analogs from the substituted human hormones.

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